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On pins and needles: Will COVID-19 vaccines 'save the world'?

Innovators are sprinting to develop inoculations against the novel coronavirus. Here, we summarize the latest information on research timelines and the potential impact of a vaccine on the pandemic—and society.

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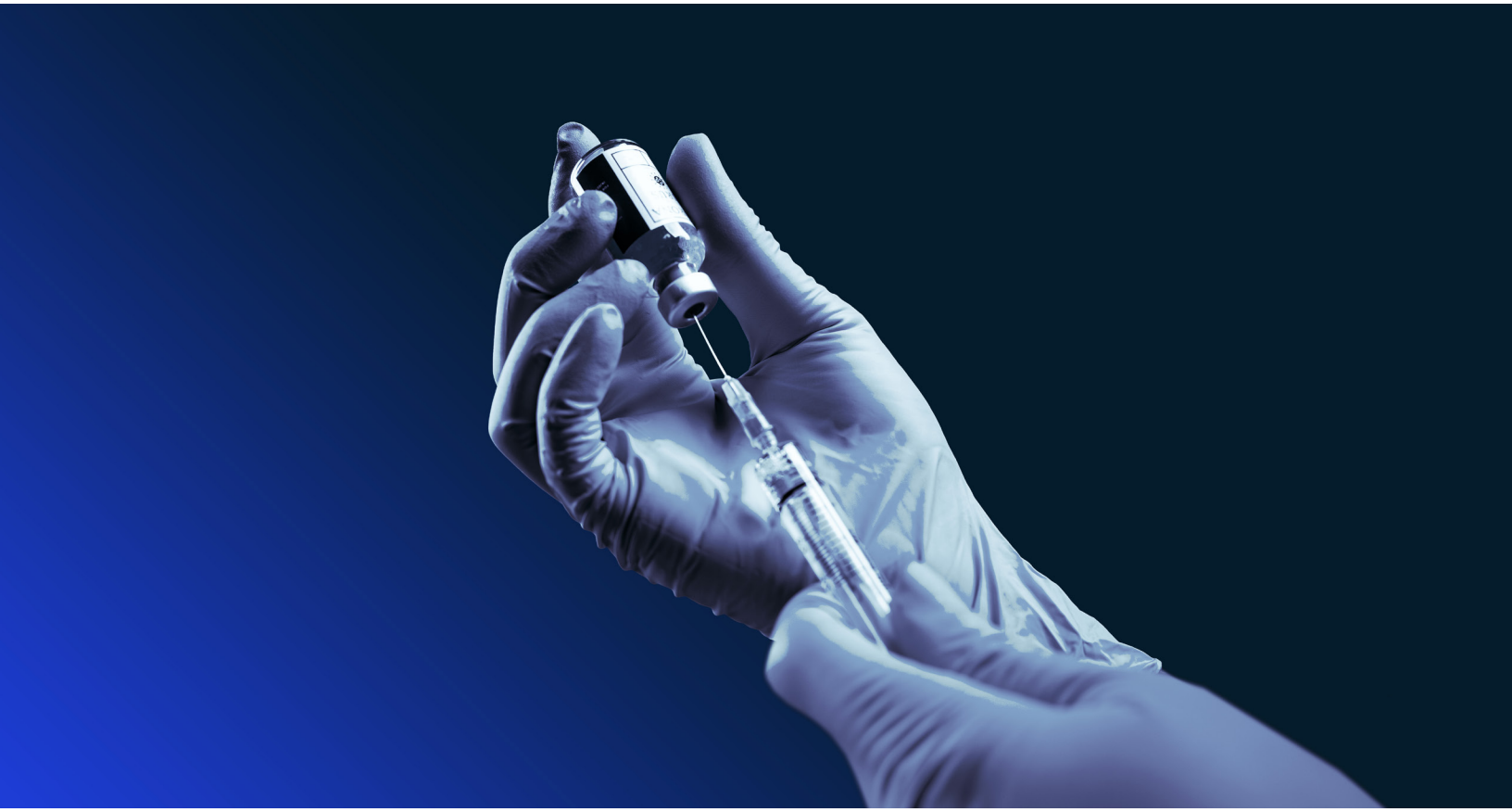


July 2020

When the novel coronavirus (SARS-CoV-2) emerged in late 2019 and began its spread around the world, the global innovation community mobilized quickly to initiate the development of a vaccine for COVID-19, the disease it causes. Hundreds of individuals and institutions—in academia, biotechnology, government, and pharmaceuticals—embarked on one of the most consequential scientific endeavors in living memory. Funding poured in from governments, multilateral agencies, not-for-profit institutions, and the private sector. Regulators showed uncanny speed in working with innovators. Now, months later, more than 250 vaccine candidates are being pursued globally, with 30 already in clinical studies and another 25 or so poised to enter human trials in 2020.

As the novel coronavirus continues to spread (with roughly 1.5 million new cases of COVID-19 globally each week) and the pursuit of a vaccine intensifies, debate has grown among corporate leaders, economists, public-policy makers, and scientific experts—and even in our own living rooms. Will we have a COVID-19 vaccine? If so, when? And how much value can it provide to society?

To bring more clarity to the conversation, we conducted an in-depth review of the COVID-19-vaccine pipeline and the range of potential immunization and demand scenarios. We looked at publicly available information on the potential time to develop COVID-19 vaccine candidates compared to other vaccines, as well as potential barriers. We spoke with experts in epidemiology and public health, as well as important participants in the vaccine ecosystem (among them, developers, funders, and government organizations). We synthesize that body of research and analysis in this article. Our goal wasn't to judge whether vaccine development should be accelerated or not; ensuring that safety protocols are being followed and outcomes are being rigorously monitored is of the utmost importance.

Here is what we found:

— Vaccine developers and government officials are publicly reporting timelines for potential emergency use of vaccine candidates between the fourth quarter of 2020 and the first quarter of 2021.

— The early data on vaccine safety and immunogenicity in Phase I and II trials are promising—although in a limited number of subjects to date.

— The discrete characteristics of the virus, the sheer number of development efforts, and innovators' unprecedented access to funding all provide reasons to believe that a COVID-19 vaccine can be developed faster than any other vaccine in history. (It took four years to develop the mumps vaccine, which was previously the fastest developed novel vaccine.[1]) More than 50 candidates are expected to enter human trials in 2020, and 250 total vaccine candidates are being pursued. Historical attrition rates would suggest that such a pipeline could yield more than seven approved products over the next few years.

— A number of hurdles remain, including validating unproven platform technologies, demonstrating vaccine candidates' safety and protection against COVID-19, and delivering the highest-impact vaccine profiles.

— Regulatory bodies are still finalizing guidelines for COVID-19 vaccines. Recent guidance from the US Food and Drug Administration (FDA), for example, suggests the need for more data prior to granting Emergency Use Authorizations (EUAs). Details are still being worked out.

— Vaccine manufacturers have announced cumulative capacity that could produce as many as one billion doses by the end of 2020 and nine billion doses by the end of 2021.

[1] Nancy Fliesler, "Getting to a COVID-19 vaccine as fast and as safely as possible," June 12, 2020, Discoveries, discoveries.childrenshospital.org.

There has been unprecedented activity around the development of a COVID-19 vaccine. The first vaccine candidate was created 42 days after the genetic sequencing of the novel coronavirus.

Taken together, all the evidence suggests that COVID-19 vaccines are likely to become available for focused populations somewhere between the fourth quarter of 2020 and the first quarter of 2021. The ultimate role they will play in the world's response to the pandemic will depend on a range of factors—for instance, the disease's epidemiology and transmission, the duration of immunity from natural infection, the profile of vaccines, and the availability of complementary therapeutics and diagnostics. It's assumed, however, that vaccines will play an important role in most response scenarios and may "save the world" in worse scenarios. In all scenarios, vaccines will serve as an insurance policy against continued health and economic shocks from the pandemic.[2]

What isn't up for debate is that business leaders, governments, and policy makers will need to continually monitor and respond to those exogenous factors.

Depending on their roles, participants in the vaccine ecosystem must be prepared to focus on some combination of the following six critical actions: adapt to a range of demand scenarios; ensure that manufacturing is flexible and fungible; understand that multiple vaccines may play different roles over time; collaborate with others to drive vaccine delivery, adoption, and monitoring; prepare now to support uptake of a vaccine; and consider endemic and postpandemic time horizons when making decisions.

Focusing on those tasks today can help stakeholders build the capacity and response system required to address not just the COVID-19 pandemic but also any future pandemics.

A question of timing: Will we have a vaccine, and if so, when?

Developers are under an unprecedented level of scrutiny as they move their vaccine candidates into clinical trials—not so surprising when you consider how many experts have tied the availability of a COVID-19 vaccine to the world's return to "a semblance of previous normality."[3] Experts have proposed a range of potential timelines, with some speculating that a vaccine will be available by the end of 2020 and others arguing it may take 12 months longer, at least, to bring a COVID-19 vaccine to market. What follows is an overview of publicly available evidence of vaccine timelines, promising early evidence from Phase I and II clinical trials, and several other virus-specific and innovation-related development factors.

Developers' and government officials' publicly available timelines

Given the sheer number of potential COVID-19 vaccines in development and the public statements from several developers, it seems likely that one will be available in the United States between the fourth quarter of 2020 and the first quarter of 2021, with more following throughout the year—potentially granted under the FDA's EUA guidelines.[4] Under that

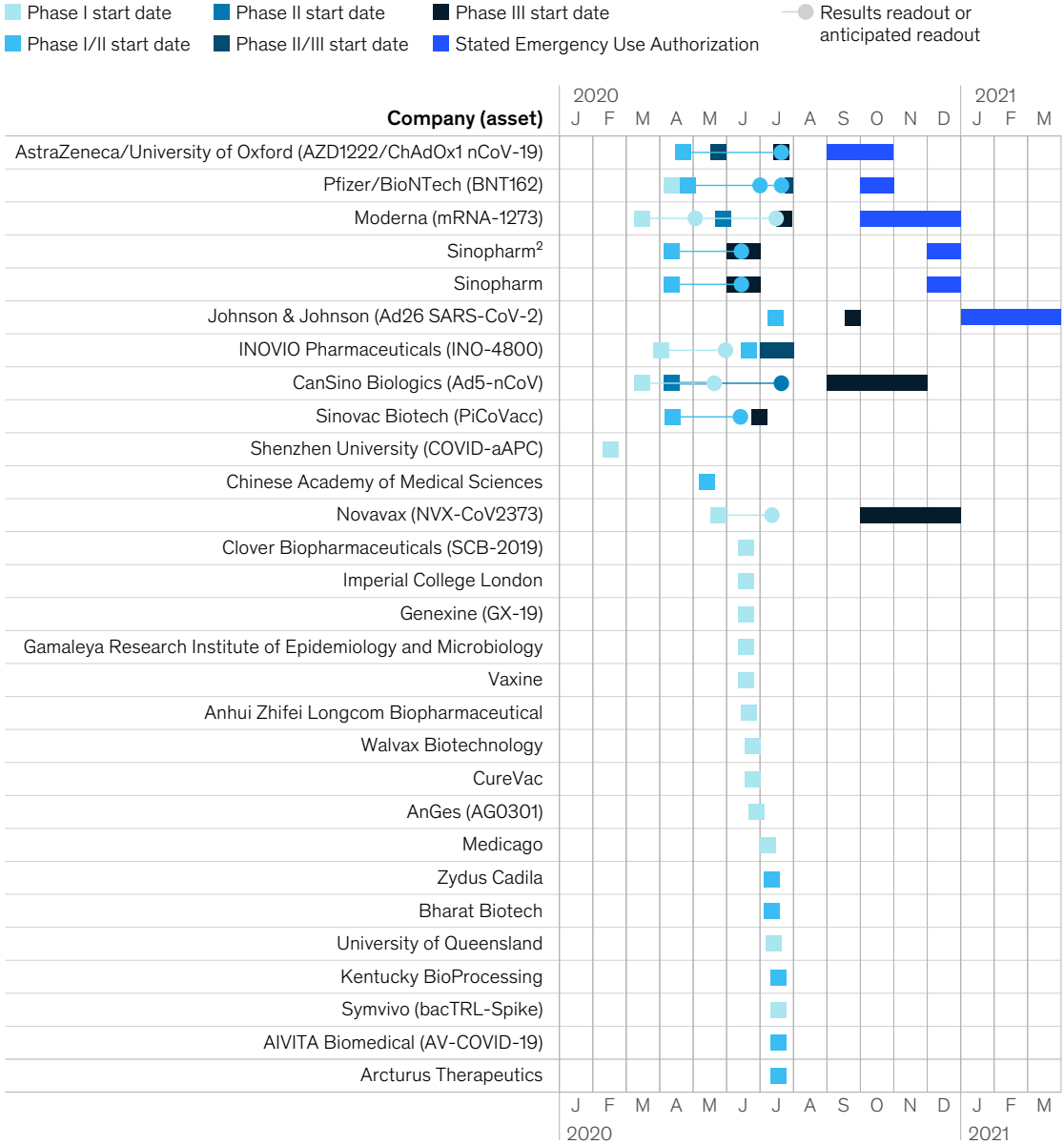
[2] Assuming that an estimated $10 billion to $15 billion in total global investment in a vaccine can prevent an estimated $10 trillion to $15 trillion in global economic shock.
[3] Lawrence Corey et al., "A strategic approach to COVID-19 vaccine R&D," *Science*, May 29, 2020, Volume 368, Number 6494, pp. 948–50, science.sciencemag.org.
[4] "Emergency Use Authorization," US Food and Drug Administration, July 10, 2020, fda.gov.

authority, the FDA "may allow unapproved medical products or unapproved uses of approved medical products to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by CBRN [chemical, biological, radiological, and nuclear] threat agents when there are no adequate, approved, and available alternatives." Similar approvals are being sought by companies in China and Europe: at least five large vaccine developers have announced that they intend to submit applications for EUA, or the local equivalent, for their candidates before the end of 2020 (Exhibit 1).

Exhibit 1

A review of the COVID-19 vaccines pipeline reveals robust development efforts.

Announced clinical-trial timelines for COVID-19-vaccine candidates[1]



[1]When the announced start date is given as a range, start dates are shown across multiple months. The first start date is listed if multiple trials are in the same phase. Includes vaccines under Emergency Use Authorization.
[2]China National Pharmaceutical.
Source: BioCentury; ClinicalTrials.gov; Milken Institute COVID-19 Treatment and Vaccine Tracker; press search

Government officials have also publicly stated that a vaccine could be approved by the end of 2020 or early in 2021. As Dr. Anthony Fauci, director of the US National Institute of Allergy and Infectious Diseases, recently said, "… by the end of this calendar year and the beginning of 2021, I feel optimistic. Nobody guarantees, but I feel optimistic that we will have a vaccine, one or more, that we can start distributing to people."[5]

Early evidence from Phase I and II clinical trials

Several companies have released data from Phase I and Phase II clinical trials that are promising:

— *In June,* Sinovac Biotech released preliminary results from a Phase I/II trial of its candidate, citing the induction of neutralizing antibodies in more than 90 percent of people who were tested 14 days after receiving two injections two weeks apart, with no severe adverse events reported.[6] China National Pharmaceutical (known as Sinopharm) presented interim readouts from a Phase I/II trial of its candidate in the same month, claiming that 100 percent of participants who received two doses over 28 days developed neutralizing antibodies.[7]

— *In early July,* Pfizer and BioNTech published preliminary results from a Phase I clinical trial of their candidate, indicating that "geometric mean neutralizing titers reached 1.8- to 2.8-fold that of a panel of COVID-19 convalescent human sera."[8] In that same time frame, Moderna published interim data from a Phase I trial of its vaccine candidate, demonstrating that 41 of 41 vaccinated participants developed neutralizing antibody titers using both a live virus and a pseudovirus assay. Across dose levels, titers were either comparable to or above those seen in a panel of convalescent sera. The geometric mean titers post-boost at the 100 microgram dose were between 2.1- and 4.1-fold higher than those seen in convalescent sera.[9]

— *In mid-July,* AstraZeneca published interim data from a Phase I/II trial of its vaccine candidate, indicating that a single dose resulted in a fourfold increase in antibodies in 95 percent of participants one month after injection.[10] Also in that time frame, CanSino Biologics published interim Phase II data for its vaccine candidate, demonstrating that a single dose induced antibodies in more than 85 percent of participants and a T-cell response within 14 days of receiving the vaccine.[11]

Further data on those and other vaccine candidates are needed, but initial results point to the idea that candidates are developing neutralizing antibodies to some degree—a potential indicator of efficacy.

Reasons to believe in accelerated development of a COVID-19 vaccine

A closer look at three key development factors—the novel coronavirus's underlying characteristics, the unprecedented size of the vaccine pipeline and number of technology platforms being used, and greater access to funding—points to the potential for the accelerated development and approval of a COVID-19 vaccine, faster than any other vaccine in history.

Virus characteristics

Unlike some families of viruses, such as HIV and the one related to seasonal influenza, coronaviruses overall have been shown to mutate at relatively low to moderate rates. The MERS-causing coronavirus, for instance, hasn't mutated substantially since it was detected in the population in 2012.[12] In fact, early data suggest that the novel coronavirus is

[5] Judy Woodruff, "How Fauci says the U.S. can get control of the pandemic," PBS, July 17, 2020, pbs.org.
[6] Adam Feuerstein, "Sinovac says early data show its Covid-19 vaccine generated immune responses," STAT, June 14, 2020, statnews.com.
[7] "Unblinding of Phase I/II clinical study of China bio-new inactivated vaccine," China Biotechnology, June 16, 2020, cnbg.com.
[8] Mark J. Mulligan et al., "Phase 1/2 study to describe the safety and immunogenicity of a COVID-19 RNA vaccine candidate (BNT162b1) in adults 18 to 55 years of age: Interim report," medRxiv, July 1, 2020, medrxiv.org.
[9] "Moderna announces publication in *The New England Journal of Medicine* of interim results from Phase 1 study of its mRNA vaccine against COVID-19 (mRNA-1273)," July 14, 2020, modernatx.com.
[10] Pedro M. Folegatti et al., "Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial," *Lancet*, July 20, 2020, thelancet.com.
[11] Feng-Cai Zhu et al., "Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in healthy adults aged 18 years or older: a randomised, double-blind, placebo-controlled, phase 2 trial," *Lancet*, July 20, 2020, thelancet.com.
[12] Stanley Perlman, "Another decade, another Coronavirus," New England Journal of Medicine, February 20, 2020, Volume 382, pp. 760–2, nejm.org.

mutating at a rate four times slower than that of the virus causing seasonal influenza.[13] Some evidence is emerging that mutations are affecting the transmission of COVID-19, but so far these appear to have had a minimal effect on antigenicity.[14] Such mutation patterns are advantageous for vaccine developers, as they alleviate the complexities associated with designing a vaccine for a moving target. Speed is of the essence, of course: all viruses always have the potential to mutate and evolve, particularly the longer they are in circulation in the population.

The sustained attack rate of the disease may allow developers to assess vaccine efficacy rapidly in Phase III. Some developers are seeking to conduct clinical trials of their COVID-19-vaccine candidates in those regions that have seen recent upticks in infection rates, such as Brazil, India, and parts of the United States, including Arizona, Florida, and Texas.[15]

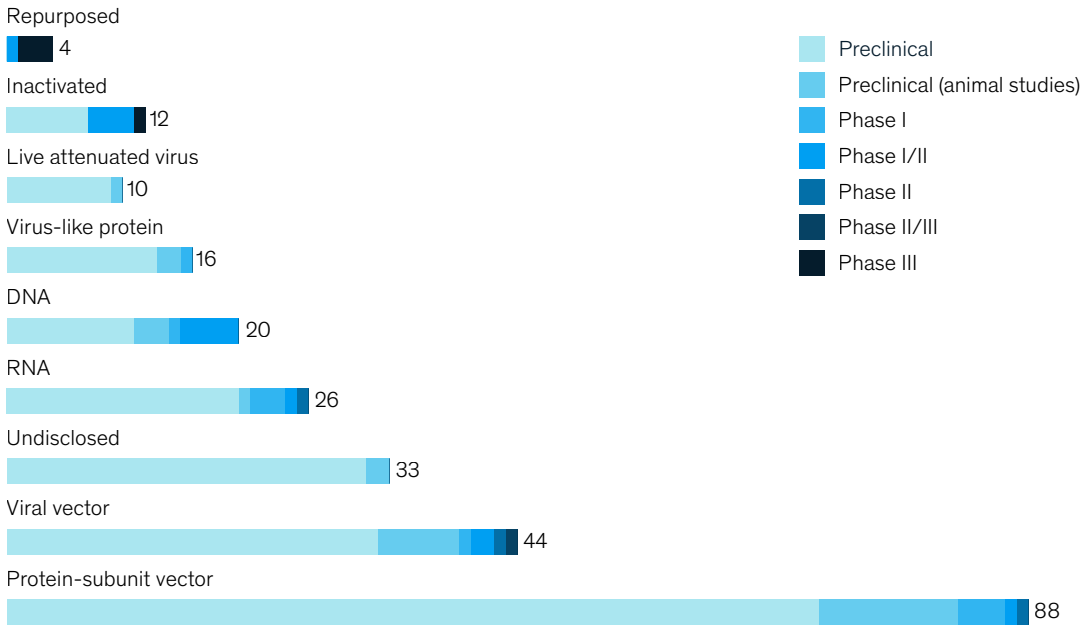
Pipeline and technology platforms

There has been unprecedented activity around the development of a COVID-19 vaccine. The first vaccine candidate was created 42 days after the genetic sequencing of the novel coronavirus. At the time of publication, there are more than 250 announced candidates globally, with more than 50 planned entries into human clinical trials in 2020 (Exhibit 2). What's more, the candidates have incorporated a broad range of technologies, from

Exhibit 2

There are more than 250 COVID-19-vaccine candidates in development globally.

Vaccine candidates by technology platform and development phase



Source: BioCentury; ClinicalTrials.gov; Milken Institute COVID-19 Treatment and Vaccine Tracker; press search

[13] Niema Moshiri, "Coronavirus seems to mutate much slower than seasonal flu," Live Science, April 6, 2020, livescience.com.
[14] Lizhou Zhang et al., "The D614G mutation in the SARS-CoV-2 spike protein reduces S1 shedding and increases infectivity," bioRxiv, June 12, 2020, biorxiv.com.
[15] Jared S. Hopkins and Peter Loftus, "Coronavirus researchers compete to enroll subjects for vaccine tests," *Wall Street Journal*, July 5, 2020, wsj.com.

proven vaccine platforms (such as protein-subunit and viral vectors) to novel ones (such as messenger RNA and DNA). Of the candidates that companies intend to enter into trials this year, more than 30 are already in human studies, according to data from clinical trial registries.

To get a better sense of the likely number of successful candidates, we reviewed key development factors plus the historical probabilities of success in vaccine development. Our analysis, based on the existing pool of announced candidates, suggests that between seven and nine vaccines could obtain regulatory approval within the next two years. Under more optimistic scenarios, that number increases to more than 20 vaccines.

In our analysis, we accounted for differences in development timelines and in the platform technologies being used. If a vaccine candidate isn't starting a clinical trial until 2021, for example, it may face funding or trial-recruitment challenges that could delay timelines. It may therefore have a lower likelihood of success. And vaccine candidates that are using novel technology platforms in their development may have a hard time succeeding if those platforms end up failing more broadly compared to other candidates (see sidebar, "Chances of success").

Access to funding

COVID-19-specific vaccines have received more funding than any prior vaccine whether developed under business-as-usual or pandemic scenarios. Public records show that from 2003 to 2014, the US National Institute of Allergy and Infectious Diseases invested a total of $221 million in the development of an Ebola vaccine. By contrast, the institute received $1.5 billion in the first six months of 2020 to support efforts to develop a COVID-19 vaccine.[16] Governments, nongovernmental organizations, and private companies are making similar monetary commitments, with a substantial portion of the funds being directed toward individual vaccine candidates.[17] Our analysis suggests that global investment in COVID-19 vaccines to date has totaled at least $6.7 billion.

Potential hurdles to overcome

The breadth and depth of the pipeline for COVID-19-vaccine candidates and the unprecedented level of investment in their development suggest that a vaccine may be on the near-term horizon. But there are still challenges to overcome—three in particular, according to our research: validating unproven platform technologies, demonstrating protection against COVID-19, and targeting the appropriate vaccine design.

Vaccine developers and government officials report that COVID-19 vaccines are likely to become available for focused populations between the fourth quarter of 2020 and the first quarter of 2021.

[16] "Supplemental appropriations bolster NIAID's COVID-19 response," National Institute of Allergy and Infectious Diseases, May 20, 2020, niaid.nih.gov.
[17] "Germany to spend €750 million on coronavirus vaccine," Deutsche Welle, May 11, 2020, dw.com.

Chances of success

In evaluating the COVID-19 vaccines currently in the pipeline, we considered two factors that could affect their probability of success: the extent of pipeline progression and the platform performance (exhibit).

For the extent of pipeline progression, we evaluated a scenario in which only those vaccines that have already announced an intent to start human trials in 2020 (56 in total) would advance through clinical development, as well as a scenario in which all announced candidates (253) progress.

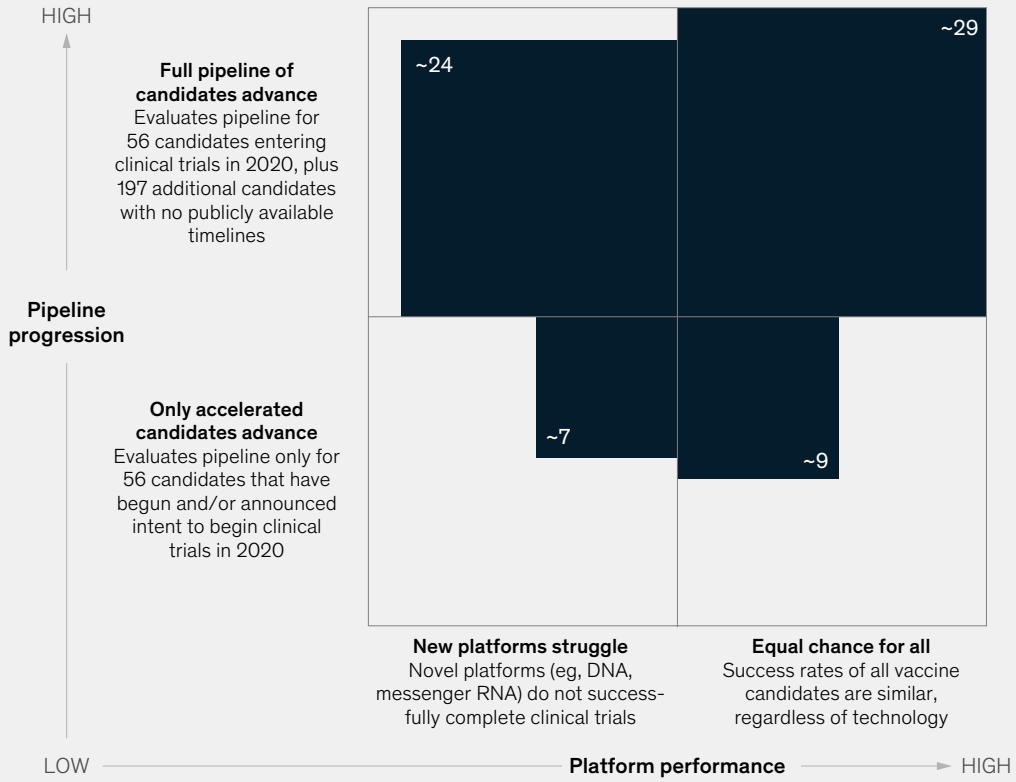
For the platform performance, we evaluated a scenario in which all candidates (regardless of the technology platform used) would have an equal chance of success, as well as a conservative scenario in which all novel vaccine platforms (for example, DNA and messenger RNA) fail to complete clinical trials successfully.

We assumed that assets would progress through the pipeline at historical rates. Preclinical assets successfully progress to Phase I of clinical trials 60 percent of the time.[1] We assumed that clinical-stage candidates would successfully progress from Phase I to Phase II at a rate of 56.15 percent, from Phase II to Phase III at a rate of 42.68 percent, from Phase III to filing at a rate of 66.27 percent, from filing to approval at a rate of 97.96 percent, and from approval to launch at a rate of 98.00 percent.[2] We counted vaccines in multi-phase trials as currently sitting in the earlier phase. For instance, a vaccine in Phase II/III would be considered at Phase II success rates. In this scenario, we assumed that

Exhibit

Two factors can help reveal vaccines' potential for success.

Potential vaccine success rate, based on historical success rate, number of successful candidates



[1] *CMR International Pharmaceutical R&D Factbook*, Clarivate, 2019, discover.clarivate.com.
[2] Pharmaprojects, Informa, 2019, pharmaintelligence.informa.com; McKinsey analysis.

Chances of success (continued)

novel technology platforms would have the same chances of success as platforms with previously approved vaccines. Last, we assumed that the type of developer (for instance, industry sponsored or academic) would have no bearing on the chances of success. The potential timing implications for various vaccines did not factor into our calculations. We did not look at when vaccine candidates might get approvals.

It's important to note that there are many other considerations that could affect how many and which vaccines are approved. For example, a number of the candidates currently in development are targeting the spike protein of the virus. However, if the spike protein mutates in such a way that vaccines already in development are no longer effective, the approval rates could be lower.

This analysis does not take into account the discontinuation of vaccine candidates because of business considerations. Nor does it factor in the challenge of developing a vaccine after the first few candidates are approved—for instance, a scenario in which head-to-head (vaccine versus placebo) trials may be needed, which would necessitate larger trials that may be more challenging to finance and recruit for.

— *Validating unproven platform technologies.* Several of the technologies—for example, DNA and messenger RNA—being used to develop COVID-19-vaccine candidates hold unique advantages over traditional platforms, the chief one being their ability to accelerate development time.[18] However, those platforms are largely unproven: there are no licensed vaccines for humans that have been approved using them. Questions remain regarding the long-term safety of the new modalities, as well as the degree to which they can induce a strong and lasting immunity response. As a result, they may face greater regulatory scrutiny compared with more established technology platforms.

— *Demonstrating protection against COVID-19.* Before a COVID-19 vaccine reaches the market—through either emergency-use or full regulatory approval—its developer will of course need to demonstrate that the vaccine candidate confers protection against the disease. Regulators require such evidence so they can have confidence in the efficacy of a vaccine candidate and potentially give high-risk populations early access to it. Vaccine developers will need to establish a sufficient indicator of protection—for example, demonstrating that the candidate provokes a certain level of antibody response in immunized individuals and then separately showing that antibodies confer protection against viral infection for a certain window of time (through assays or animal-transfer models).

In addition, COVID-19-vaccine developers will need to design and conduct late-stage clinical trials in a way that enables them to demonstrate the full efficacy of their vaccine candidates rapidly. For instance, they may want to enrich site selection for clinical trials, targeting regions in which COVID-19 hasn't had prior high attack rates (thus, with fewer exposed trial participants) but in which attack rates would rise after participants had been immunized. That way, they could rapidly assess the efficacy of the vaccine candidate being tested.

— *Targeting the appropriate vaccine design.* One of the outstanding questions for COVID-19-vaccine developers is to what degree the novel coronavirus will mutate around the spike protein, which latches onto cells and transmits the virus through cell membranes. While there has been limited significant mutation within the novel coronavirus to date, future changes to the spike protein itself could affect the relevance of the vaccine candidates currently in development, as most innovators have designed them around the spike protein. If mutations did occur and candidates needed to be revisited, it would obviously create delays for a successful vaccine launch.

[18] Jamie Bell, "Moderna timeline: How the biotech firm has moved alongside pharma giants in Covid-19 vaccine race," Clinical Trials Arena, June 8, 2020, clinicaltrialsarena.com.

Regulatory considerations

Regulators have been contemplating the appropriate guidelines to assess all the evidence that will be arriving imminently on vaccine candidates. Before the end of 2020, a few innovators should have limited data sets for safety and immunogenicity. Given the low mortality rates for COVID-19 among the general population, it remains to be seen whether regulators will deem clinical trial data collected in 2020 sufficient for the deployment of the vaccine in certain high-risk populations. Recent guidelines by the FDA suggest that vaccine candidates will need more data to be granted EUA—but even that decision will likely depend on a number of factors, including how convincing the data are, how the pandemic evolves, and the risk–benefit assessment of the vaccine in a broader context.

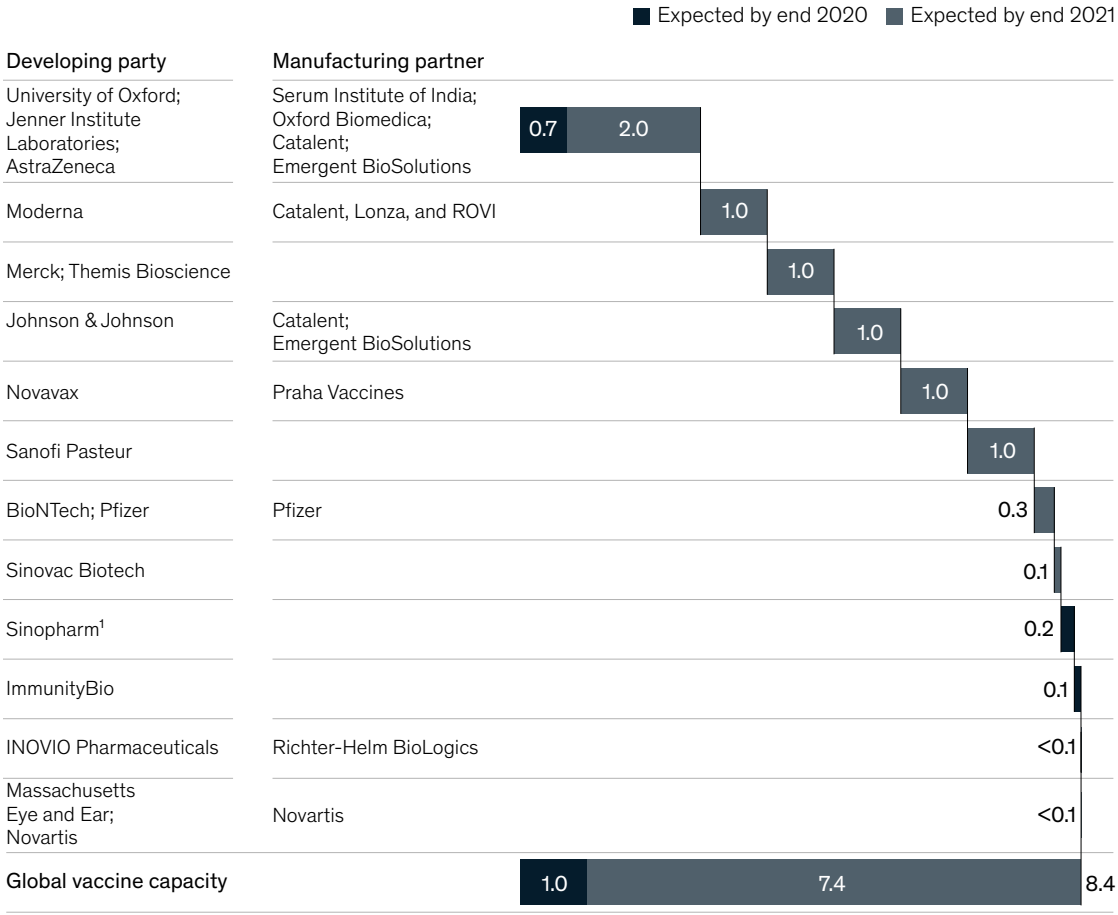
Capacity considerations

To date, several manufacturers have announced capacity plans that total about one billion COVID-19 vaccine doses by the end of 2020 and eight billion to nine billion doses by the end of 2021 (Exhibit 3). Not all of their vaccines will be successful, of course, but this industry announcement is an encouraging

Exhibit 3

Some developers are building greater capacity into their vaccine-manufacturing processes.

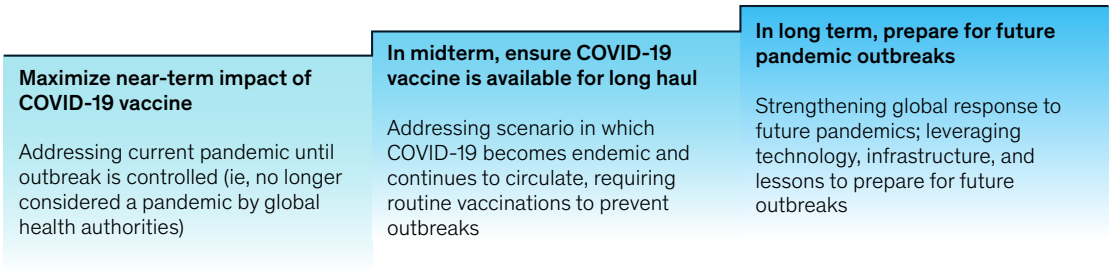
Announced manufacturing capacity for vaccine candidates, billions of doses



[1]China National Pharmaceutical.
Source: BioCentury; ClinicalTrials.gov; Milken Institute COVID-19 Treatment and Vaccine Tracker; press search

Exhibit 4

A COVID-19 vaccine could provide value for society over three time horizons.



sign that when candidates are approved there will be capacity to reach various patient populations now and over time.

In total, the evidence base suggests it is likely that some COVID-19-vaccine candidates will be available between the fourth quarter of 2020 and the beginning of 2021. The initial set of approved candidates is likely to be small, for use in specific patient groups, and supply may be constrained. Later in 2021, additional candidates on other technology platforms could receive approval and be manufactured on a broader scale and approved for broader populations.

A question of value: How will a vaccine affect society?

Another issue up for debate is the potential value of a COVID-19 vaccine to the global community. How important is a vaccine for overcoming the health-related effects of COVID-19 and its associated effects on the global economy? We attempt to contextualize the importance of vaccine-development efforts over three time horizons: near term, in the current COVID-19 pandemic; midterm to longer term, in which COVID-19 becomes endemic or requires revaccination (for example, because of waning protection or strain mutation); and longer term, looking at global-pandemic preparedness beyond the COVID-19 crisis (Exhibit 4).

In the near term, COVID-19 vaccines would prevent more people from becoming infected and dying. The second-order effects include controlled utilization of hospitals and healthcare resources, the development of herd immunity, and gradual economic recovery. In the midterm, if COVID-19 were to become endemic, the presence of a vaccine would allow the broader population to be inoculated (as with other standard immunizations, such as those for the seasonal flu and for measles, mumps, and rubella). And if the disease mutates or immunity is short lived, the additional development and manufacturing capacity currently being established could be applied quickly to increase vaccine supply, create new vaccines, and accelerate the response to future pandemics.

The profile of a valuable vaccine

In the near term, a COVID-19 vaccine's value to society will be determined by four factors: the vaccine's profile, the disease-attack rate, the duration of natural immunity, and complementary therapeutics and testing (Exhibit 5).

Exhibit 5

Four factors will determine the value of a COVID-19 vaccine to society.

		Lower value of vaccine	Higher value of vaccine
	Vaccine profile	Unfavorable product profile: ● Low level of protection (eg, <50% efficacy) ● Limited duration of immunity (eg, <1 year) ● Distribution challenges (eg, short shelf life, complex cold chain) ● Inconvenient administration (eg, complex or novel devices, multiple doses)	Optimal product profile: ● High level of protection (eg, >70% efficacy) ● Extended duration of immunity (eg, >3 years) ● Simple logistics/distribution (eg, long shelf life, thermostable at room temperature) ● Convenient administration (eg, oral, single dose)
Vaccine context	**Natural immunity duration**	Long-term natural immunity: ● Extended duration (eg, lifetime) ● Slow virus mutation	Short-term natural immunity: ● Limited duration (eg, <12 months) ● Accelerated virus mutation
	Therapeutics and testing	Breakthrough therapeutics and diagnostics: ● Breakthrough therapeutics available at scale, especially for early stage and prevention ● Breakthrough testing available at scale	Limited therapeutics and diagnostics: ● Limited therapeutics available for COVID-19 treatment or prevention ● Marginal improvement of testing, with limited availability
	Epidemiology	Extreme attack rate: ● High R_0[1] (leading to herd immunity) or low R_0 (virus naturally waning down)	Moderate attack rate: ● Moderate R_0 (continuous infection without reaching herd immunity)

[1]Basic reproduction number.

The most valuable COVID-19 vaccines will be the ones that can be administered once, have 100 percent effectiveness, and provide immunity for years. Of course, based on what we know about vaccine development historically, achieving that type of vaccine profile would be like finding the proverbial needle in a haystack. Developers face many challenges in getting to that perfect state. Vaccines must be able to be manufactured and distributed at sufficient scale. Limited supply could force policy makers into tough decisions about who receives a vaccine first. And onerous methods of vaccine distribution or administration—for instance, if they require cryoshipping or a complex delivery device—could limit usage rates in geographies that lack the necessary infrastructure.

The value of a COVID-19 vaccine will also be influenced by the disease's rate of attack. If viral-transmission rates drop significantly, the need for a vaccine is obviated. If they accelerate, populations may achieve natural herd immunity and thus in most cases no longer require immunization. However, if the rates remain at current (moderate) levels, there will likely be an acute need for vaccines to control infection rates.

The length of natural immunity conferred to recovered individuals will be another critical determinant of a vaccine's value. If the duration is in line with that of the vaccine for seasonal influenza, individuals who were infected and recovered in the first wave of the COVID-19 pandemic will still require vaccination to protect against future outbreaks.

Of course, if one of the more than 250 COVID-19 therapeutics currently in development prove particularly effective at treating the disease, there could actually be *reduced* demand for a vaccine. More widespread testing may lead to earlier identification of COVID-19-positive individuals, further dampening the transmission of the disease and allowing for early treatment to improve outcomes, thus reducing the burden on the healthcare system.

Near-term vaccine demand

Given all the value-determination factors, what could the overall near-term demand for COVID-19 vaccines look like? Our research reveals three potential scenarios for vaccine demand, all of which warrant consideration by government agencies, nongovernmental organizations, pharmaceutical companies, and vaccine manufacturers (Exhibit 6).

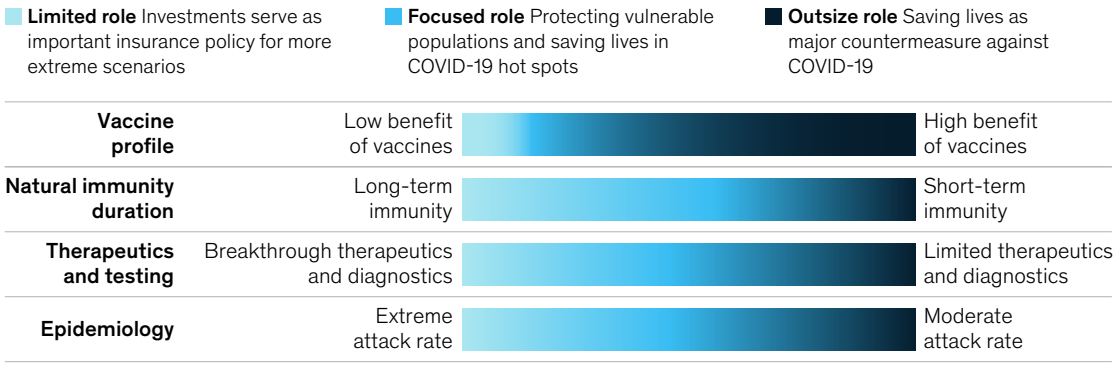
At one end of the spectrum, vaccines are viewed as critical components of the solution to the COVID-19 crisis. They serve as the primary countermeasure against COVID-19, driven by sustained, moderate viral-transmission rates; limited duration of immunity (either natural or vaccine induced); few effective therapeutics; and favorable product profiles.

In a more moderate scenario, vaccines have a focused role, with the demand still significant, albeit lower. For example, if transmission rates remain stable, the duration of immunity from a vaccine is about three to five years, and the availability of therapeutics and testing improve, the broad-scale need for vaccines is less acute. However, a COVID-19 vaccine could still be used to protect vulnerable populations (such as healthcare workers and immunocompromised patients) and to address hot spots that could emerge in future waves.

Exhibit 6

A vaccine may have a limited, focused, or outsize role in global recovery from the COVID-19 pandemic.

Vaccine impact by factor



At the other end of the spectrum, in a scenario in which COVID-19 transmission wanes and breakthrough therapeutics against the disease emerge, a vaccine has a somewhat limited role, serving as more of an insurance policy for society. There would likely be more focused demand for a vaccine in this scenario (for example, for use in high-risk populations), but the investment made to develop and scale the COVID-19 vaccine would be considered protection from a more severe outbreak.

A question of preparedness

Clearly, there is momentum behind global innovators' vaccine-development efforts. Experts agree there is a strong likelihood of a vaccine coming to market in the next six to 12 months, and an even stronger indication that an effective COVID-19 vaccine can create outsize value for global citizens, economies, and healthcare systems. With all that in mind, there are six actions that stakeholders in the vaccine ecosystem can take as they continue with development, manufacturing, policy making, implementation, and other efforts.

1. Adapt to a range of demand scenarios

As noted, a variety of scenarios can emerge that will affect the demand for a potential vaccine. Governments, distributors, manufacturers, regulators, and other stakeholders should build contingency plans to react and adapt successfully. Such plans should take into account the three scenarios cited earlier, the potential vaccine candidates that could be approved, and the corresponding distribution and access requirements of those vaccines.

2. Ensure that manufacturing is flexible and fungible

Vaccine innovators are already factoring manufacturing decisions into their development processes much earlier than they ever have. As noted, several manufacturers have announced capacity plans that total about one billion doses by the end of 2020 and eight billion to nine billion doses by the end of 2021. But the reality is that some candidates will fail and some capacity plans may be delayed.

Developers and funding partners need to build flexibility and fungibility into their manufacturing processes and networks. Companies should also plan for how they might redirect capacity—whether internal capacity or that gained through bilateral partnerships—to other promising vaccines. Developers must be open to new types of partnerships, even with competitors, in some cases. In addition to private-company manufacturing, public partnerships are emerging to increase manufacturing capacity and expand further the global access to a vaccine.[19]

3. Understand that multiple vaccines may play different roles over time

As we have noted, different vaccines will be available and scaled at different periods in the next six to 24 months. Experts agree we are unlikely to see a single vaccine, including the earliest ones, with all the ideal vaccine characteristics, so health officials, policy makers, and regulators will need to consider carefully the juxtaposition of the multiple vaccines they have in development and how they complement one another. For instance, a vaccine that is safe, has moderately high efficacy, and conveys several months of immunity could play an important role in allowing people to get back to work, thereby kick-starting a global economic recovery. Future vaccines with improved efficacy profiles may then complement vaccines that were approved earlier.

4. Collaborate to drive delivery, adoption, and monitoring

Innovators are experienced in designing, developing, testing, and manufacturing a safe and effective vaccine, but if the vaccine isn't shipped, distributed, and administered in a thoughtful way, innovators' efforts may be in vain. Multiple organizations are already working on frameworks to ensure global access to vaccines, which will be a top priority. In most demand scenarios, the speed and size of

[19] "Gavi launches innovative financing mechanism for access to COVID-19 vaccines," Gavi, June 4, 2029, gavi.org.

Several manufacturers have announced capacity plans that total about one billion COVID-19 vaccine doses by the end of 2020 and eight billion to nine billion by the end of 2021.

the vaccine rollout—potentially in the billions of doses—will be unprecedented. It will be important for stakeholders to take an end-to-end view of their roles; that is, from product shipment, to healthcare provider consultations, to vaccine administration.

Different vaccines have different logistical needs, including dosing schedules, site of administration, and cold-chain requirements. DNA-based vaccines, for instance, are traditionally shelf stable at normal temperatures, while RNA-based, protein subunit, and viral vectors require cold chain or cryoshipping. As with manufacturing, stakeholders should consider working with partners to develop logistical plans contingent upon the various demand scenarios. They should, for instance, consider how individuals will receive the vaccine and what other efforts that may entail—for example, can it be administered in a retail setting by a nurse practitioner or only in a physician's office?

Providers and other stakeholders should also consider establishing nerve centers in various geographies to coordinate the implementation of their vaccine programs. They should be prepared to adapt to different logistical requirements of the vaccines that receive approval, based on the outcomes of early clinical trials. Stakeholders should also consider the implications of multiple approved vaccines that may be launched in the same country at the same time but require different logistical considerations.

Stakeholders will need to jointly monitor vaccine rollout, as well. Vaccine developers should establish tracking programs for their products that are built on real-world evidence. Providers and developers should consider partnering to address any overlaps in monitoring—for instance, they could work to integrate product barcodes with electronic-medical-record systems.

5. Prepare now to support uptake of a vaccine
Stakeholders will need to provide key pieces of infrastructure to support the uptake of COVID-19 vaccines. For instance, insurers will need to address coverage issues for the most vulnerable populations—enabling global access to vaccines, limiting out of pocket expenses, and so on. Given the recent hesitancy to vaccinate seen in many countries around the world, healthcare and public-sector leaders may also need to mount educational campaigns that provide accurate information about new vaccines and increase public confidence. Recent polls suggest that only about 30 percent of individuals in the United States would be willing to be immunized if a COVID-19 vaccine were available in the near term.[20]

6. Consider endemic and postpandemic time horizons when making decisions
Innovators, manufacturers, and other key stakeholders should take a long-term view of each of the vaccine candidates in the pipeline and consider how decisions taken today could shape their relevance in the postpandemic

[20] Linda Y. Fu, Natalie J. Pudalov, and Sarah Schaffer DeRoo, "Planning for a COVID-19 Vaccination Program," *JAMA*, June 2020, Volume 323, Number 24, pp. 2458–9, jamanetwork.com.

world—especially given that one of the likely scenarios includes COVID-19 becoming endemic to some countries. In addition to ensuring that the adaptations made today will be relevant in the future, that strategy will likely make the trickle-down effects for broader preparedness become more clear. Investments made now may create opportunities for greater preparedness for future pandemics and affect the ability to onboard capacity for new vaccine technologies and platforms when they might be needed.

The timing question is becoming a bit more clear, as is the question of how much value may be created by the global launch of successful vaccines against COVID-19. Based on the established set of facts, experts agree a vaccine for COVID-19 is likely to be available somewhere between the fourth quarter of 2020 and first quarter of 2021, most likely for use in specific populations, with additional candidates coming on line by the end of 2021. In most scenarios, a vaccine will serve as a means to ensure immunity in broader populations. At a minimum, continued investment in vaccines can serve as a critical insurance policy needed to expedite the move to the next normal. Over time, lessons from the development of a COVID-19 vaccine can be built into future plans to accelerate other vaccine-development efforts.

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